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Intravenous Immunoglobulin Treatment of Respiratory Syncytial Virus Infections in Infants and Young Children

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Respiratory syncytial virus (RSV)-infected cotton rats (*Sigmadon hispidus*) and owl monkeys (*Aotus trivirgatus*) showed significant reductions in RSV shedding from their respiratory tracts following parenteral therapy with human intravenous immunoglobulin (IVIG) containing high titers of RSV-neutralizing antibody. Because this therapy was well tolerated and appeared safe, a double-blind, placebo-controlled IVIG immunotherapy pilot study was performed on 35 hospitalized, RSV-infected infants and children. The treatment was well tolerated and resulted in significant reductions in nasal RSV shedding and in improvements in transcutaneous oximetry readings. However, the mean duration of hospitalization was not reduced by IVIG treatment. Followup to date has revealed no harmful effects resulting from immunotherapy of RSV infections. These studies appear to refute the hypothesis that passively acquired antibody may exacerbate RSV bronchiolitis or pneumonia in infants. Studies with larger numbers of seriously ill children will be required to determine if immunoglobulin G immunotherapy of RSV infections in infants is of clinical value.

Respiratory syncytial virus (RSV) is an important respiratory pathogen of infants and young children. The virus produces annual epidemics of bronchiolitis and pneumonia in children throughout the world and causes numerous hospital admissions, substantial morbidity, and some mortality (2, 5, 7, 15, 17, 30, 31). Efforts to produce an effective vaccine for prevention of these infections have thus far been unsuccessful (16, 19, 35). Only recently, with the introduction of ribavirin, has treatment other than supportive therapy been available for children with serious RSV infections (1, 6, 11, 12, 29, 32).

The current studies were prompted by a series of observations: (i) pups of RSV-immune cotton rat mothers were protected from RSV infection, presumably by transplacental antibody (25); (ii) injection of serum from RSV-immune cotton rats protected nonimmune cotton rats from RSV infection (26); (iii) high-titered RSV-immune human serum and human immunoglobulin prepared for intravenous administration (IVIG) were effective for both prophylaxis and therapy of RSV infections in cotton rats and owl monkeys (13, 24); (iv) some lots of human IVIG contained substantial titers of neutralizing antibody to RSV (14); and (v) careful pathological studies of the lungs of RSV-infected animals treated with IVIG revealed no evident microscopic pulmonary abnormalities characteristic of the formation of antigen-antibody complexes or other untoward pulmonary reactions (13, 24). The current study was designed to determine if IVIG containing substantial levels of RSV-neutralizing antibody could be safely administered and if it would hasten clinical recovery when infused into RSV-infected, hospitalized children.

MATERIALS AND METHODS

Institutional review. The protocols for these studies were reviewed and approved by the Institutional Review Committees of Children's Hospital National Medical Center. Authorization was initially given to study 10 randomly chosen patients with the intent that permission would be granted to study additional patients once the clinical and laboratory courses and the outcomes for the first 10 patients has been reviewed and if no adverse clinical or laboratory findings were noted.

Selection of patients. Children enrolled in the study were admitted to Children's Hospital National Medical Center for treatment of pneumonia or bronchiolitis, were likely to be hospitalized for 4 or more days, weighed 10 kg or less, had nasal and pharyngeal swab specimens in which RSV antigens were detected by indirect immunofluorescence, and had informed consent given by their parents. Exclusion criteria included congenital heart disease, inability to establish an intravenous line, failure to obtain informed consent from at least one parent, and previously known hypersensitivity to blood products.

Study plan. (i) Study drug. Every lot of human IVIG that we examined contained variable titers of neutralizing antibody to RSV (14). Several lots of IVIG (Sandoglobulin), licensed for clinical use in the United States, were screened to determine their neutralizing-antibody titers (21). The two lots chosen for these studies were free of human immunodeficiency virus antibody and had geometric mean neutralizing-antibody titers of approximately 1:5,000. Lyophilized human albumin, prepared in identical bottles and with protein concentrations identical to that of the IVIG, was used as the placebo drug in these studies. Each bottle, IVIG or

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placebo, was reconstituted to a 6% protein concentration with sterile normal saline before use.

(ii) Study design. The study was a double-blind, placebo-controlled trial. Random patient numbers for the study were generated before the entry of any patients. Patients were assigned to one of two equal-size treatment groups based on a table of random numbers. Only the study monitors (Sandoz Inc., East Hanover, N.J.) knew the contents of the bottles of drug infused into each participant. The codes were not broken until the completion of each portion of the study.

(iii) Treatment plan. Each patient received 2 g of drug (IVIG or albumin placebo) per kg of body weight administered over 12 to 24 h. Pulse, temperature, blood pressure, and respiratory rate were observed prior to infusion and at 1, 4, and 12 h after infusion was begun. There was a daily physical examination and recording of vital signs. The severity of each symptom was scored on an analog scale of 0 to 4 (0, no symptoms).

(iv) Data collection during hospitalization. On the day of hospital admission, the following laboratory and clinical assessments were performed: medical history, physical examination, oropharyngeal-nasal washes for virus cultures and RSV titration, oropharyngeal swabs for indirect immunofluorescence studies to detect RSV antigens, pulse or transcutaneous oximetry, serum glutamic oxalacetic transaminase, total serum protein, serum creatinine, blood urea nitrogen, complete blood count (including platelet and reticulocyte counts), and chest X ray. Arterial-blood gas determinations were done only if clinically indicated. Serum was stored for later measurements of immunoglobulin G (IgG), RSV neutralization, and tetanus antibody titers. The baseline tetanus antibody titers were part of an analysis to determine whether IVIG would suppress the immune responses of the infants to tetanus toxoid immunization (33). On the day after completion of drug infusion (day 1), the following laboratory and clinical assessments were carried out: oropharyngeal-nasal washes for RSV titration, transcutaneous oximetry, collection of serum for IgG and RSV-neutralizing-antibody titers, and detailed assessments of the clinical status of the patient. Thereafter, the oximetry results, RSV titers, and clinical statuses of the patients were monitored daily until the time of discharge. Admission clinical assessments and severity scoring (12, 29) were performed only by either of two experienced investigators (W.R. or H.W.K.) to ensure consistency. Laboratory and clinical assessments performed at discharge were physical examination, oropharyngeal-nasal washes for RSV titration, whole blood collection for T- and B-lymphocyte counts and mitogenesis studies (performed only on the first five children treated with IVIG and the first five treated with albumin), oximetry, complete blood count, serum glutamic oxalacetic transaminase, bilirubin, creatinine, blood urea nitrogen, RSV-neutralizing-antibody titers, and chest X ray.

(v) Data collection after discharge. About 6 weeks after discharge, each child underwent an outpatient assessment to determine general health status, and blood was obtained for complete blood count, quantitative IgG, RSV-neutralizing-antibody titers, and tetanus antibody titers. Seven children had serum obtained after their second diphtheria-pertussis-tetanus (DPT) immunization injection and 6 weeks after their third DPT immunization.

Laboratory procedures. Blood counts, serum glutamic oxalacetic transaminase, creatinine, blood urea nitrogen, and T- and B-cell counts and mitogenesis were performed by standard laboratory procedures. RSV antigens in cells from nasal swabs were detected by previously published fluorescent-antibody procedures (18). Quantitative RSV titers in HEp-2 cell cultures were determined by previously published methods (2). IgG levels were determined by radial immunodiffusion with commercial kits (Meloy Laboratories, Springfield, Va.). RSV neutralization tests were performed by a 60% plaque reduction assay (21, 28). Transcutaneous oximetry was performed daily on each child with an N100 pulse oximeter (Nelcor). All oximeter measurements were done after the children had been breathing room air for at least 20 min.

Statistical analysis. Statistical analysis was performed by the two-way analysis of covariance with the change from base line as the dependent variable and the base-line value as the covariate or concomitant variable. The analysis is based on two assumptions: (i) there is homogeneity of treatment-study-specific slopes, and (ii) the common slope is significantly different from zero. Two-sided tests were used.

RESULTS

When no evidence of IVIG-induced immune suppression was seen, as determined by counts and mitogenic proliferative responses of T and B lymphocytes in the first 10 children, the Institutional Review Committees permitted enrollment of additional patients. Thus, 21 patients were enrolled during the 1984 to 1985 respiratory season (December to March), and an additional 14 were enrolled during the 1985 to 1986 season, for a total of 35 patients. The original goal of 70 patients was not met because of logistical problems unrelated to the responses of the patients to IVIG or placebo treatment.

Each infant or child was enrolled after RSV antigens were detected in exfoliated nasopharyngeal cells by indirect immunofluorescence. RSV was successfully cultured from admission samples in every case. The IVIG infusions were well tolerated. Complete 2-g/kg infusions were not completed in three patients, two IVIG treated and one placebo, because of problems maintaining venous access. IgG levels rose in both of these IVIG-treated children (from 708 to 2,880 mg/dl and from 563 to 2,779 mg/dl), suggesting receipt of most of the planned dose. Neutralization titers rose commensurately in both infants. Counts of T and B lymphocytes and pokeweed- and phytohemagglutinin-driven mitogenesis studies performed at hospital discharge revealed no differences in responses among the 10 initial patients (5 on IVIG and 5 on placebo). The mean ages (± standard deviation) of the two groups were similar (on IVIG, 4.4 ± 4.3 months; on placebo, 4.4 ± 4.1 months). Pretreatment quantitative IgG levels and RSV-neutralizing-antibody titers were also similar.

On day 1 following the completion of therapy, RSV-neutralizing-antibody titers and IgG levels were significantly

TABLE 1. Geometric mean titers of serum RSV-neutralizing antibody and total IgG levels in IVIG-treated versus placebo-treated children with RSV infections

Treatment (no. of patients)	Antibody titer[a]		IgG level (mg/dl)	
	Before[b]	After[c]	Before[b]	After[c]
IVIG (17)	114 ± 115	877 ± 341[d]	406 ± 195	2,095 ± 562[d]
Placebo (18)	109 ± 148	119 ± 141	387 ± 211	366 ± 178

[a] Reciprocal of geometric mean.
[b] Drawn before initiation of IgG or albumin infusion.
[c] Drawn within 24 h of conclusion of infusion.
[d] $P < 0.001$ (± standard deviation)

increased in the IVIG-treated group (Table 1). The IVIG-treated group had significantly greater reductions in nasopharyngeal RSV infectivity titers ($P < 0.01$) and significant improvements in transcutaneous oximetry results ($P < 0.05$) compared with albumin-treated controls (Tables 2 and 3). Complete clearance of RSV before discharge was observed in 13 (77%) of 17 IVIG-treated children, compared with 9 (50%) of 18 albumin-treated children. Though more of the treated children were RSV negative compared with the controls, the differences were not significant ($P = 0.11$). No significant differences were found between hematology values, serum glutamic oxalacetic transaminase levels, or chest X-ray findings for the two groups. Some infants in both groups experienced transient rises in total serum protein levels, urine specific gravities, and blood urea nitrogen levels (the highest blood urea nitrogen level recorded was 14 mg/dl). Treatment did not exacerbate pneumonia or bronchiolitis in any patient of either group. One infant was readmitted to Children's Hospital National Medical Center shortly after discharge, and a diagnosis of cystic fibrosis was made. Followup was terminated for one infant killed in an airplane accident shortly after discharge.

Followups completed for 30 of the 35 children at 6 weeks and 1 year yielded no evidence that IVIG-treated children were later more susceptible to subsequent RSV or other respiratory infections. Seven patients, four placebo treated and three IVIG treated, received at least two DPT immunizations in the months following hospitalization. Tetanus antibody titers were 1:20 or lower in pretreatment serum of all seven patients; three had undetectable titers. At 6 weeks following the third DPT immunization, all seven patients had titers of 1:10 or greater.

No significant differences were observed between the IVIG-treated and the placebo-treated groups in the following: supplemental oxygen requirements, duration of hospitalization (3.94 versus 3.06 days, respectively), or duration of clinical symptoms such as sneezing, wheezing, rhonchi, rales, retractions, nasal discharge, or nasal obstruction. Neither group included infants who required admission to an intensive care unit or needed ventilatory support, though such patients were not excluded by the protocol.

DISCUSSION

Hall (10) reviewed the enigma surrounding the role of the host immune response in the severity of lower-respiratory-tract infections caused by RSV in infants. Evidence was cited (5, 19) that immune complexes (type 3 reactions), IgE mediation (type 1 reactions), and cell-mediated cytotoxicity (type 4 reactions) may each have a role in the augmentation of RSV lung disease in infants. In cotton rat studies performed prior to the inception of the present study, we found evidence that the enhancement of pulmonary pathology in RSV-infected recipients of a Formalin-inactivated RSV vaccine resulted from an action of Formalin on RSV (27). It was demonstrated (25, 28) that RSV immunity in cotton rats correlated with neutralizing-antibody levels. Further, human serum or purified IgG (24) could be used successfully in immunoprophylaxis or immunotherapy of RSV infections in cotton rats. No type 3 reactions were observed in the lungs of animals naturally immune or passively immunized with cotton rat or human IgG when they were challenged with RSV.

In a large epidemiological study, Parrott and co-workers observed that, though most severe RSV disease occurred in infants less than 6 months of age, there was some sparing from illness of infants less than 2 months of age, a period when passively acquired maternal IgG-RSV antibodies are present in largest amounts (23). More recently, several workers have demonstrated an apparent protective effect of transplacental antibody in newborns, as measured in serum or cord blood (8, 20, 22, 34). Bruhn and Yeager (3) found no correlation between cord blood complement fixation RSV antibody and the severity of disease in RSV-infected infants.

Once there was convincing evidence that humoral immunity protected against rather than accentuated RSV disease in infants, immunotherapy of RSV infections was examined in animal models. RSV-infected cotton rats (24) and owl monkeys were treated with human IVIG (13). In these animals, highly significant reductions in the amounts of RSV recovered from lungs or tracheal lavage specimens were observed. The therapy was also well tolerated. Careful histologic examination of the lungs of RSV-infected, IgG-treated animals revealed no evidence of antibody-induced, enhanced disease. The results from the use of Formalin-inactivated RSV vaccine in the cotton rat (27), RSV immunotherapy in the cotton rat (24), owl monkey studies (13), and the demonstration of substantial RSV antibody titers in licensed human IVIG preparations (14) suggested that a trial of IgG immunotherapy in RSV-infected infants should be done.

The findings in the current trial confirm that human IgG, which had substantial levels of RSV-neutralizing antibody, was well tolerated and safe when infused into RSV-infected infants and young children. We observed no evidence of disease exacerbation or prolongation, and the high doses of IgG (2 g/kg) did not appear to induce physiologic problems. The short hospital stays suggest that most infants studied were not critically ill. The infusions resulted in significant increases in IgG levels and titers of circulating RSV-neutralizing antibody. Significant changes were also observed in the amounts of RSV recovered by titration from nasopharyngeal secretions and in levels of oxygen saturation as determined by transcutaneous oximetric measurements in the IVIG-treated children. Followup of 86% of the children,

TABLE 2. Initial titers and daily mean reductions (expressed as 50% tissue culture infective dose per 0.2 ml, $\log_{10}$) in nasal wash specimens from IVIG-treated or placebo-treated children with RSV infections

Treatment	RSV titer before treatment, mean ± SD (no. of patients)	Mean RSV titer reduction after treatment (no. of patients) on day: 1	2[a]	3	4[b]
IVIG	3.71 ± 1.69 (17)	2.00 (17)	3.10 (16)	2.73 (13)	2.87 (8)
Placebo	2.93 ± 1.33 (18)	1.52 (18)	2.36 (18)	2.37 (10)	3.21 (5)

[a] $P < 0.01$ for differences compared by two-way analysis of covariance with change from base line as the dependent variable and the base line as the covariate variable.
[b] Most patients were discharged between hospital days 3 and 4.

TABLE 3. Differences (increase or reduction) in mean pO_2[a] oximetry values for IVIG-treated versus placebo-treated children with RSV infections

Treatment	pO_2 (no. of patients) before treatment	Mean change in pO_2 (no. of patients) on treatment day: 1[b]	2	3
IVIG	72.27 (15)	7.28 (15)	6.57 (14)	9.58 (11)
Placebo	79.71 (17)	−7.07 (17)	2.24 (17)	3.41 (9)

[a] In millimeters of mercury.
[b] $P < 0.05$ for differences compared by two-way analysis of covariance.

for as long as 2 years for some (16 of the first 21 patients), has thus far detected no evident long-term sequelae from the treatment. Furthermore, the three IVIG-treated infants who were subsequently immunized with DPT responded as well as placebo-treated children did to the tetanus antigen.

Ribavirin (1-beta-D-ribofuranosyl-1-1,2,4,-triazole-3-carboxamide) is the treatment of choice for children hospitalized with serious RSV infections. Ribavirin variably reduces RSV shedding from the respiratory tract, improves oxygenation, and hastens clinical recovery (1, 6, 11, 12, 29, 32). The responses measured in our patients, i.e., reduction in RSV shedding and improvement of transcutaneous oximetry, were similar to those observed in the ribavirin studies. As ribavirin and IgG inhibit RSV replication by different mechanisms, studies seem indicated to determine if combination therapy may be more effective than either alone. A recent report (9) of combined immunoglobulin and ribavirin treatment of RSV-infected cotton rats supports this approach.

In summary, the intravenous infusion of IVIG into infants and young children with documented RSV infections was well tolerated. Bronchiolitis or pneumonia was not exacerbated. Significant improvements in oxygenation and reductions in RSV shedding from the respiratory tract suggest that this method of treatment should be further studied with IgG with higher RSV antibody titers in children with more serious RSV disease and perhaps in combination with ribavirin.

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